

**Claims**

1. A method for treating a subject having, or at risk of having, a disorder which can be treated by increased vasoconstriction or inhibition of vasodilation, comprising:

administering to a subject in need of such treatment an agent that up-regulates EDG  
5 receptor signaling in an amount effective to treat the disorder.

2. The method of claim 1, wherein the agent is a sphingosine kinase activator.

3. The method of claim 2, wherein the sphingosine kinase activator is selected from the  
10 group consisting of TNF- $\alpha$ , EGF and PDGF.

4. The method of claim 1, wherein the agent is an EDG receptor agonist.

5. The method of claim 4, wherein the EDG receptor agonist is selected from the group  
15 consisting of EDG-1 receptor agonist, EDG-3 receptor agonist, EDG-5 receptor agonist and EDG-8 receptor agonist.

6. The method of claim 4, wherein the EDG receptor agonist is an EDG-3 receptor  
20 agonist.

7. The method of claim 4, wherein the EDG receptor agonist is selected from the group  
consisting of sphingosine-1-phosphate, dihydro-sphingosine-1-phosphate, a sphingosine-1-  
phosphate analog, psychosine, sphingosylphosphorylcholine and lysophosphatidic acid.

8. The method of claim 4, wherein the EDG receptor agonist is selected from the group  
25 consisting of sphingosine-1-phosphate, dihydro-sphingosine-1-phosphate, and a sphingosine-  
1-phosphate analog.

9. The method of claim 1, wherein the agent is a sphingosine-1-phosphate phosphatase  
30 inhibitor.

10 The method of claim 1, wherein the disorder is one which can be treated with increased cerebral vasoconstriction or inhibition of cerebral vasodilation.

11. The method of claim 1, wherein the disorder is a migraine headache.

5 12. A method for decreasing arterial blood flow in a subject who would benefit from decreased arterial blood flow, comprising:

administering to a subject in need of such treatment an agent that up-regulates EDG receptor signaling in an amount effective to decrease arterial blood flow.

10 13. The method of claim 9, wherein the agent is a sphingosine kinase activator.

14. The method of claim 13, wherein the sphingosine kinase activator is TNF- $\alpha$ , EGF, or PDGF.

15 15. The method of claim 12, wherein the agent is an EDG receptor agonist.

16. The method of claim 15, wherein the EDG receptor agonist is selected from the group consisting of EDG-1 receptor agonist, EDG-3 receptor agonist, EDG-5 receptor agonist and  
20 EDG-8 receptor agonist.

17. The method of claim 15, wherein the EDG receptor agonist is an EDG-3 receptor agonist.

25 18. The method of claim 15, wherein the EDG receptor agonist is selected from the group consisting of sphingosine-1-phosphate, dihydro-sphingosine-1-phosphate, a sphingosine-1-phosphate analog, psychosine, sphingosylphosphorylcholine and lysophosphatidic acid.

30 19. The method of claim 15, wherein the EDG receptor agonist is selected from the group consisting of sphingosine-1-phosphate, dihydro-sphingosine-1-phosphate, and a sphingosine-1-phosphate analog.

20. The method of claim 12, wherein the agent is a sphingosine-1-phosphate phosphatase inhibitor.

21. The method of claim 12, wherein the arterial blood flow is cerebral artery blood flow.

22. The method of claim 12, wherein the subject is having, or is at risk of having, a migraine headache.

23. A method for inducing vasoconstriction in a subject who would benefit from induced vasoconstriction, comprising:

administering to a subject in need of such treatment an agent that up-regulates EDG receptor signaling in an amount effective to induce vasoconstriction.

24. The method of claim 23, wherein the agent is a sphingosine kinase activator.

25. The method of claim 24, wherein the sphingosine kinase activator is TNF- $\alpha$ , EGF, or PDGF.

26. The method of claim 23, wherein the agent is an EDG receptor agonist.

27. The method of claim 26, wherein the EDG receptor agonist is selected from the group consisting of EDG-1 receptor agonist, EDG-3 receptor agonist, EDG-5 receptor agonist and EDG-8 receptor agonist.

28. The method of claim 26, wherein the EDG receptor agonist is an EDG-3 receptor agonist.

29. The method of claim 26, wherein the EDG receptor agonist is selected from the group consisting of sphingosine-1-phosphate, dihydro-sphingosine-1-phosphate, a sphingosine-1-phosphate analog, psychosine, sphingosylphosphorylcholine and lysophosphatidic acid.

30. The method of claim 26, wherein the EDG receptor agonist is selected from the group consisting of sphingosine-1-phosphate, dihydro-sphingosine-1-phosphate, and a sphingosine-1-phosphate analog.

5 31. The method of claim 23, wherein the agent is a sphingosine-1-phosphate phosphatase inhibitor.

32. The method of claim 23, wherein the vasoconstriction is cerebral vasoconstriction.

10 33. The method of claim 23, wherein the subject is having, or is at risk of having, a migraine headache.

34. A method for treating a subject having, or at risk of having, a disorder which can be treated by increased vasodilation or inhibition of vasoconstriction, comprising:  
15 administering to a subject in need of such treatment an agent that down-regulates EDG receptor signaling in an amount effective to treat the disorder.

35. The method of claim 34, wherein the agent is a sphingosine kinase inhibitor.

20 36. The method of claim 35, wherein the sphingosine kinase inhibitor is selected from the group consisting of methylsphingosine, N,N-dimethylsphingosine, trimethylsphingosine, D,L-threo-dihydrosphingosine, high density lipoprotein, and 3-fluoro-sphingosine analogues.

37. The method of claim 34, wherein the agent is an EDG receptor inhibitor.

25 38. The method of claim 37, wherein the EDG receptor inhibitor is selected from the group consisting of EDG-1 receptor inhibitor, EDG-3 receptor inhibitor, EDG-5 receptor inhibitor, and EDG-8 receptor inhibitor.

30 39. The method of claim 37, wherein the EDG receptor inhibitor is an EDG-3 receptor inhibitor.

40. The method of claim 37, wherein the EDG receptor inhibitor is sphingosine or suramin.

41. The method of claim 34, wherein the in agent is a sphingosine-1-phosphate phosphatase activator.

42. The method of claim 34, wherein the disorder is selected from the group consisting of stroke, subarachnoid hemorrhage and cerebral vasospasm.

43. A method for increasing arterial blood flow in a subject who would benefit from increased arterial blood flow, comprising:  
administering to a subject in need of such treatment an agent that down-regulates EDG receptor signaling in an amount effective to increase arterial blood flow.

44. The method of claim 43, wherein the agent is a sphingosine kinase inhibitor.

45. The method of claim 44, wherein the sphingosine kinase inhibitor is selected from the group consisting of methylsphingosine, N,N-dimethylsphingosine, trimethylsphingosine, D,L-threo-dihydrosphingosine, high density lipoprotein, and 3-fluoro-sphingosine analogues.

46. The method of claim 43, wherein the agent is an EDG receptor inhibitor.

47. The method of claim 46, wherein the EDG receptor inhibitor is selected from the group consisting of EDG-1 receptor inhibitor, EDG-3 receptor inhibitor, EDG-5 receptor inhibitor and EDG-8 receptor inhibitor.

48. The method of claim 46, wherein the EDG receptor inhibitor is an EDG-3 receptor inhibitor.

49. The method of claim 46, wherein the EDG receptor inhibitor is sphingosine or suramin.

50. The method of claim 43, wherein the in agent is a sphingosine-1-phosphate phosphatase activator.

51. The method of claim 43, wherein the subject is having, or is at risk of having, a stroke,  
5 a subarachnoid hemorrhage or a cerebral vasospasm.

52. The method of claim 43, wherein the arterial blood flow is cerebral artery blood flow.

53. The method of claim 43, further comprising co-administering a second agent to the  
10 subject with a condition treatable by the second agent in an amount effective to treat the condition, whereby the delivery of the second agent to a tissue of the subject is enhanced as a result of the increased arterial blood flow.

54. The method of claim 53, wherein the second agent is selected from the group  
15 consisting of analeptic, analgesic, anesthetic, adrenergic agent, anti-adrenergic agent, amino acids, antagonists, antidote, anti-anxiety agent, anti-cholinergic, anti-convulsant, anti-depressant, anti-emetic, anti-epileptic, anti-hypertensive, anti-fibrinolytic, anti-hyperlipidemia, anti-migraine, anti-nauseant, anti-neoplastic (brain cancer), anti-obsessional agent, anti-obesity agent, anti-parkinsonian, anti-psychotic, appetite suppressant, blood  
20 glucose regulator, cognition adjuvant, cognition enhancer, dopaminergic agent, emetic, free oxygen radical scavenger, glucocorticoid, hypocholesterolemic, hypolipidemic, histamine H2 receptor antagonists, immunosuppressant, inhibitor, memory adjuvant, mental performance enhancer, mood regulator, mydriatic, neuromuscular blocking agent, neuroprotective, NMDA antagonist, post-stroke and post-head trauma treatment, psychotropic, sedative,  
25 sedative-hypnotic, serotonin inhibitor, tranquilizer, and treatment of cerebral ischemia, calcium channel blockers, free radical scavengers - antioxidants, GABA agonists, glutamate antagonists, AMPA antagonists, kainate antagonists, competitive and non-competitive NMDA antagonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, sodium- and calcium-channel blockers, and potassium channel openers.

30 55. The method of claim 53, wherein the second agent is TPA.

56. A method for inhibiting vasoconstriction in a subject who would benefit from inhibited vasoconstriction, comprising:

administering to a subject in need of such treatment an agent that down-regulates EDG receptor signaling in an amount effective to inhibit vasoconstriction.

57. The method of claim 56, wherein the agent is a sphingosine kinase inhibitor.

58. The method of claim 57, wherein the sphingosine kinase inhibitor is selected from the group consisting of methylsphingosine, N,N-dimethylsphingosine, trimethylsphingosine, D,L-threo-dihydrosphingosine, high density lipoprotein, and 3-fluoro-sphingosine analogues.

59. The method of claim 56, wherein the agent is an EDG receptor inhibitor.

60. The method of claim 59, wherein the EDG receptor inhibitor is selected from the group consisting of EDG-1 receptor inhibitor, EDG-3 receptor inhibitor, EDG-5 receptor inhibitor and EDG-8 receptor inhibitor.

61. The method of claim 59, wherein the EDG receptor inhibitor is an EDG-3 receptor inhibitor.

62. The method of claim 59, wherein the EDG receptor inhibitor is sphingosine or suramin.

63. The method of claim 56, wherein the agent is a sphingosine-1-phosphate phosphatase activator.

64. The method of claim 56, wherein the subject is having or is at risk of having a stroke, a subarachnoid hemorrhage or a cerebral vasospasm.

65. The method of claim 56, wherein the vasoconstriction is cerebral vasoconstriction.

66. A method for identifying an agent that regulates vasoconstriction, comprising:  
selecting an agent that binds to sphingosine kinase, and

determining whether the agent that binds to sphingosine kinase modulates vasoconstriction,

wherein a change in vasoconstriction in the presence of the agent is indicative of an agent that regulates vasoconstriction.

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67. A method for identifying an agent that regulates vasoconstriction comprising:  
selecting an agent that binds to an EDG receptor, and  
determining if the agent that binds to the EDG receptor modulates vasoconstriction  
wherein a change in vasoconstriction in the presence of the agent is indicative of an  
agent that regulates vasoconstriction.

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68. A method for identifying an agent that regulates vasoconstriction comprising:  
selecting an agent that binds to a sphingosine-1-phosphate phosphatase, and  
determining if the agent that binds to a sphingosine-1-phosphate phosphatase  
modulates vasoconstriction  
wherein a change in vasoconstriction in the presence of the agent is indicative of an  
agent that regulates vasoconstriction.

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69. A pharmaceutical preparation comprising  
an agent that up-regulates EDG receptor signaling in an effective amount to treat a  
disorder which can be treated by increased vasoconstriction or inhibition of vasodilation, and  
a pharmaceutically-acceptable carrier.

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70. The pharmaceutical preparation of claim 70, wherein the agent is a sphingosine kinase  
activator.

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71. The pharmaceutical preparation of claim 71, wherein the sphingosine kinase activator  
is TNF- $\alpha$  or EGF.

72. The pharmaceutical preparation of claim 70, wherein the agent is an EDG receptor  
agonist.

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The pharmaceutical preparation of claim 73, wherein the EDG receptor agonist is selected from the group consisting of EDG-1 receptor agonist, EDG-3 receptor agonist, EDG-5 receptor agonist and EDG-8 receptor agonist.

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The pharmaceutical preparation of claim 73, wherein the EDG receptor agonist is selected from the group consisting of sphingosine-1-phosphate, dihydro-sphingosine-1-phosphate, a sphingosine-1-phosphate analog, psychosine, sphingosylphosphorylcholine and lysophosphatidic acid.

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The pharmaceutical preparation of claim 70, wherein the agent is a sphingosine-1-phosphate phosphatase inhibitor.

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The pharmaceutical preparation of claim 70, wherein the disorder is a migraine headache.

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A pharmaceutical preparation comprising an agent that down-regulates EDG receptor signaling in an effective amount to treat a disorder which can be treated by increased vasodilation or inhibition of vasoconstriction, and a pharmaceutically-acceptable carrier.

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The pharmaceutical preparation of claim 78, wherein the agent is a sphingosine kinase inhibitor.

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The pharmaceutical preparation of claim 79, wherein the sphingosine kinase inhibitor is selected from the group consisting of methylsphingosine, N,N-dimethylsphingosine, trimethylsphingosine, D,L-threo-dihydrosphingosine, high density lipoprotein, and 3-fluoro-sphingosine analogues.

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The pharmaceutical preparation of claim 78, wherein the agent is an EDG receptor inhibitor.

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The pharmaceutical preparation of claim 81, wherein the EDG receptor inhibitor is selected from the group consisting of EDG-1 receptor inhibitor, EDG-3 receptor inhibitor, EDG-5 receptor inhibitor, and EDG-8 receptor inhibitor.

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The pharmaceutical preparation of claim 81, wherein the EDG receptor inhibitor is an EDG-3 receptor inhibitor.

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The pharmaceutical preparation of claim 81, wherein the EDG receptor inhibitor is sphingosine or suramin.

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The pharmaceutical preparation of claim 78, wherein the agent is a sphingosine-1-phosphate phosphatase activator.

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15 The pharmaceutical preparation of claim 78, wherein the disorder is selected from the group consisting of stroke, subarachnoid hemorrhage and a cerebral vasospasm.

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